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(54) **Title:** DIPHENYLUREA DERIVATIVES USEFUL AS ERG CHANNEL OPENERS FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

(57) **Abstract:** The present invention relates to the medical use of a certain group of diphenyl urea derivatives as ERG channel openers for the treatment of cardiac arrhythmias, and to the use of these compounds for such treatment.

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DIPHENYLUREA DERIVATIVES USEFUL AS ERG CHANNEL OPENERS FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

TECHNICAL FIELD

The present invention relates to the medical use of a certain group of diphenyl urea derivatives as ERG channel openers for the treatment of cardiac arrhythmias, and to the use of these compounds for such treatment.

BACKGROUND ART

The heart is a muscle, which pumps the blood in the circulation by contracting 1-3 times per second. The heartbeat is caused by simultaneous contraction of the individual cardiac muscle cells (cardiac myocytes). The synchronization of the cellular contraction is governed by the electrical cardiac impulse (the cardiac action potential), which is generated in the pacemaker cells of the sine node and spreads rapidly over the heart through a specific conduction system.

Disturbances in the generation of the impulse and the conduction of impulse may occur either as a consequence of a disease, a drug treatment or electrolyte imbalances. Such disturbances in the impulse are called arrhythmia or dysrythmia and they may lead to unease, emboli, syncope or sudden death.

At a molecular level a group of proteins called ion channels underlie the electrical events in the heart since they are able to conduct electrical currents across the cell membrane. Different types of ion channels are thus instrumental in the generation and conduction of the cardiac action potential, in the regulation of the heart rate by the autonomic nervous system, and in the contractile process in the individual heart cells. The different types of ion channels are therefore good targets for anti-arrhythmic cardiac drugs, and many anti-arrhythmic drugs on the market do exert their effect by interacting with ion channels.

One of the ion channels responsible for the termination of the cardiac action potential is the human ERG1 channel (Human Ether-a-go-go Related Gene channel, HERG1 channel), which is selective for permeation of potassium ions. Block of this channel caused by drugs or genetic dysfunction may lead to arrhythmia.

A number of drugs have been shown to block the ERG channels, including compounds as diverse as anti-psychotics, anti-depressants, anti-histamines and anti-biotics. Several of these drugs have been withdrawn from the market, or put on prescription, within recent years due to pro-arrhythmic effects. Pharmacological block of HERG1 channels leads to a prolongation of the cardiac action potential and a

reduced potassium conductance during the repolarisation and resting phase of the action potential. The prolonged action potential is reflected in the ECG as an increased distance between the Q and T waves, and the condition is called acquired Long QT Syndrome. Patients being treated with HERG1 blocking drugs can develop serious ventricular tachy-arrhythmia called torsade-des-pointes, which may eventually lead to syncope and possibly cardiac arrest.

HERG1 channels are targets for a number of genetic mutations giving rise to inherited Long QT Syndrome. These patients also develop serious arrhythmias of the torsade-des-pointes type as well as a number of other arrhythmias including brady-arrhythmias. The patients are currently often treated with adrenergic beta-receptor blockers or pacemakers possibly with intracardial defibrillators (ICD).

Most of the existing anti-arrhythmic drugs on the market were developed before their molecular target was known. However, for many of them their molecular target has later been shown to be an ion channel.

Anti-arrhythmic drugs are usually divided into four main classes.

Class 1 compounds all block the cardiac voltage-dependent sodium channel. Some class 1 compounds do have additional effects influencing the cardiac action potential being the basis for a further subdivision into three subclasses:

Class 1A compounds are sodium channel blockers such as Quinidine or Disopyramid, which prolong the action potential.

Class 1B compounds are sodium channel blockers such as Lidocaine, Mexiletin or Phenytoin, which shorten the action potential.

Class 1C compounds are sodium channel blockers such as Flecainid or Propafenon, which do not change the action potential duration.

Class 1 compounds interact with the sodium channel during its open or inactivated state and are dissociated from the channels during its closed state (during diastole). The rate of dissociation determines whether they show a frequency-dependent channel block. Some of the class 1 compounds also block subtypes of potassium or calcium permeable channels in addition to their sodium channel blocking effect.

Class 2 compounds are β-adrenoceptor blockers and include drugs like Atenolol, Metoprolol, Timolol or Propranolol. β-adrenoceptor blockers can be selective for cardiac β1-receptors or have affinity for β1- as well as β2-receptors. Some of the compounds have an intrinsic β-stimulating effect too.

Class 3 compounds are potassium channel blockers such as Amiodaron, which prolong the action potential by delaying repolarisation of the action potential through block of potassium channels. Class 3 compounds show lack of effects in many patients and may even be pro-arrhythmic, probably due to the destabilising effect of the reduced potassium current.

Class 4 compounds are blockers of L-type calcium channels such as Verapamil.

In addition to the compounds allocated to those four classes, Digoxin and Adenosin also find use in the treatment of arrhythmia.

WO 96/28537 describes long QT genes and methods for diagnosing or preventing the occurrence of Long QT Syndrome. WO 00/06772 describes mutations in and genomic structure of HERG1, a Long QT Syndrome gene. WO 02/42417 describes a new human ERG (HERG2) channel. WO 02/42735 describes a method of identifying HERG channel inhibitors. However, the use of HERG1 channel openers for the treatment of cardiac arrhythmias has never been suggested.

Moreover, WO 94/22807, WO 96/25157, WO 97/45400, WO 97/45111, WO 98/47879, WO 2000/24707, WO 2004/022529 and WO 2004/111017 describe urea derivatives useful as potassium channel modulators or chloride channel blockers, but an effect on HERG1 channels have not been reported with these compounds.

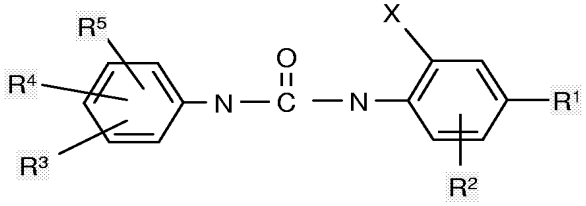
SUMMARY OF THE INVENTION

The present invention is based on the discovery that whereas dysfunction or block of human ERG channels destabilises the cardiac myocytes and delays the repolarisation we have found that an increased cardiac ERG current helps repolarise the cardiac myocytes, and stabilises the cells during the repolarising and resting phase. The increased ERG current will inhibit early and late after-depolarisations as well as on the re-entry arrhythmia mechanism. ERG channel activation therefore is found useful for the treatment of all major cardiac arrhythmias.

As described above the HERG channel openers for use according to the present invention are different from known antiarrhythmic drugs and represent a new therapeutic principle, having the advantage of both increasing the potassium currents in the vulnerable period of the action potential, and of stabilising the cardiomyocytes following this period due to slow channel closure.

Next, the present invention is based on the discovery that certain urea and benzamide derivatives are useful as ERG channel activators.

The diphenyl urea derivatives for use according to the invention may be characterised by Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

X represents hydroxy, carboxy, a tetrazolyl group, or an oxadiazolyl or a triazolyl group, which oxadiazolyl a triazolyl groups may optionally be substituted with oxo and/or hydroxy groups;

R^1 represents hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, sulfamoyl, *N,N*-dialkylsulfamoyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted once or twice with alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, nitro, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, piperazinyl-carbonyl, alkyl-piperazinyl-carbonyl, amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, sulfamoyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl;

R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl (methyl), halo (fluoro, chloro, bromo), haloalkyl (trifluoromethyl), nitro, hydroxy, alkoxy, haloalkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl (methoxy-carbonyl), amino-carbonyl, benzoyl, acetyl, phenyl, pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo (fluoro, chloro, bromo), haloalkyl (trifluoromethyl), nitro, hydroxy, alkoxy (methoxy), phenyl, pyridyl, or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo (fluoro), haloalkyl (trifluoromethyl) or nitro; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and R^5 represents hydrogen.

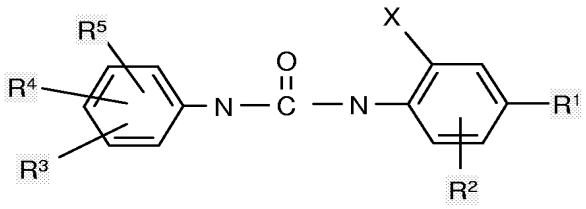
In another aspect the invention provides a method of treatment, prevention or alleviation of a cardiac disease, disorder or condition of a living animal body, including a human, which disorder, disease or condition is responsive to activation of an ERG channel, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount a compound capable of activating an ERG channel, or a pharmaceutically-acceptable addition salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Diphenyl Urea Derivatives

The diphenyl urea derivatives for use according to the invention may be characterised by Formula I or I'



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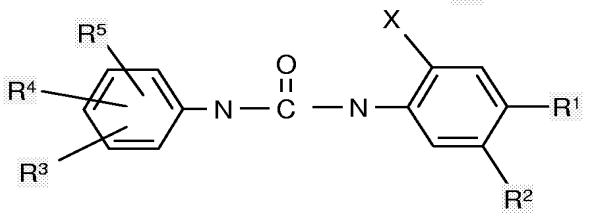


(I')

or a pharmaceutically acceptable salt thereof, wherein

X represents hydroxy, carboxy, a tetrazolyl group, or an oxadiazolyl or a triazolyl group, which oxadiazolyl a triazolyl groups may optionally be substituted with oxo and/or hydroxy groups;

R^1 represents hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, sulfamoyl, *N,N*-dialkylsulfamoyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted once or twice with alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, nitro, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, piperazinyl-carbonyl, alkyl-piperazinyl-carbonyl, amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, sulfamoyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl;

R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl (in particular methyl), halo (in particular fluoro, chloro or bromo), haloalkyl (in particular trifluoromethyl), nitro, hydroxy, alkoxy, haloalkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl (in particular methoxy-carbonyl), amino-carbonyl, benzoyl, acetyl, phenyl, pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo (in particular fluoro, chloro or bromo), haloalkyl (in particular trifluoromethyl), nitro, hydroxy, alkoxy (in particular methoxy), phenyl, pyridyl, or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo (in particular fluoro), haloalkyl (in particular trifluoromethyl) or nitro; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and R^5 represents hydrogen.

In a preferred embodiment of the invention X represents hydroxy, carboxy, a tetrazolyl group, or an oxadiazolyl or a triazolyl group, which oxadiazolyl a triazolyl groups may optionally be substituted with oxo or hydroxy groups.

In a more preferred embodiment X represents hydroxy, carboxy, a tetrazolyl group, a 1,3,4-oxadiazolyl group or a 1,2,4-triazolyl group.

In an even more preferred embodiment X represents hydroxy, carboxy, *1H*-tetrazol-5-yl, 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 4-hydroxy-1,2,4-triazol-3-yl or 3-oxo-1,2-dihydro-1,2,4-triazol-1-yl.

In a still more preferred embodiment X represents carboxy, *1H*-tetrazol-5-yl, 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 2-oxo-3H-1,3,4-oxadiazol-5-yl, 4-hydroxy-1,2,4-triazol-3-yl or 3-oxo-1,2-dihydro-1,2,4-triazol-1-yl.

In a still more preferred embodiment X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group.

In a most preferred embodiment X represents a tetrazolyl group.

In another preferred embodiment of the invention R^1 represents hydrogen, alkyl, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with alkyl, halo, haloalkyl, alkoxy, haloalkoxy, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, alkyl-piperazinyl-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl.

In a more preferred embodiment R^1 represents hydrogen, alkyl, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with alkyl, halo, haloalkyl, alkoxy, haloalkoxy, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, alkyl-piperazinyl-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl.

In an even more preferred embodiment R^1 represents hydrogen, methyl, fluoro, chloro, bromo, hydroxy, methoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, methyl-carbonyl-amino, methoxy-carbonyl, *N,N*-dimethyl acryl-amide, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with methyl, fluoro, chloro, bromo, trifluoromethyl, methoxy, trifluoromethoxy, nitro, carboxy, methoxy-carbonyl, *N,N*-dimethyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dimethyl-amino-carbonyl, *N*-methyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-

carbonyl, piperidine-1-yl-carbonyl, 4-alkyl-piperazine-1-yl-carbonyl, *N,N*-dimethyl-amino-carbonyl-ethyl, *N,N*-dialkyl acryl-amide, *N,N*-dimethyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl.

In a third preferred embodiment of the invention R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl.

In a more preferred embodiment R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl or nitro.

In an even more preferred embodiment R^2 represents hydrogen, chloro, bromo, methoxy, methoxy-carbonyl or nitro.

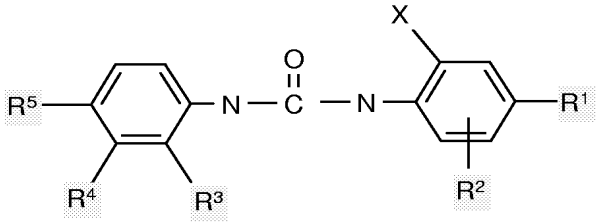
In a fourth preferred embodiment of the invention R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, haloalkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl, pyridyl, or phenyl substituted with haloalkyl; and R^5 represents hydrogen, halo, haloalkyl or nitro; or R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and R^5 represents hydrogen.

In a more preferred embodiment R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, carboxy, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, pyridyl; and R^4 represents hydrogen, halo, haloalkyl, alkoxy or phenyl; and R^5 represents hydrogen, halo, haloalkyl or nitro; or R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and R^5 represents hydrogen.

In an even more preferred embodiment R^3 represents hydrogen, methyl, fluoro, chloro, bromo, trifluoromethyl, nitro, hydroxy, carboxy, methoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl or pyridyl; and R^4 represents hydrogen, fluoro, chloro, bromo, trifluoromethyl, methoxy or phenyl; and R^5 represents hydrogen, fluoro, trifluoromethyl or nitro; or R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and R^5 represents hydrogen.

In a still more preferred embodiment R^3 represents hydrogen, methyl, fluoro, chloro, bromo, trifluoromethyl, nitro, hydroxy, carboxy, methoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl or pyridyl; and R^4 represents hydrogen, fluoro, chloro, bromo, trifluoromethyl, methoxy or phenyl; and R^5 represents hydrogen.

In a fifth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula II or II'



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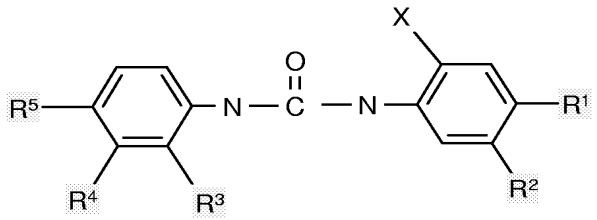


(II')

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined above; and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, or phenyl; or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo or haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and R^5 represents hydrogen.

In a preferred embodiment X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with alkyl, halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidin-1-yl-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, alkyl-piperazinyl-carbonyl, *N,N*-dialkylsulfamoyl or alkyl-piperazinyl-sulfonyl;

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen; alkyl; halo; haloalkyl; nitro; alkoxy; phenyl or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo or haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen.

In a more preferred embodiment

X represents a tetrazolyl group;

R^1 represents halo; or R^1 represents phenyl substituted with alkyl, halo, haloalkyl, *N,N*-dialkyl-amino-carbonyl, piperidin-1-yl-carbonyl, alkyl-piperazinyl-carbonyl or alkyl-piperazinyl-sulfonyl; and

R^2 represents hydrogen;

R^3 represents halo or haloalkyl;

R^4 represents hydrogen or halo; and

R^5 represents hydrogen or halo; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen.

In an even more preferred embodiment X represents 1*H*-tetrazol-5-yl;

R^1 represents bromo; or R^1 represents phenyl substituted with methyl, fluoro, chloro, trifluoromethyl, *N,N*-dialkyl-amino-carbonyl or piperidin-1-yl-carbonyl;

R^2 represents hydrogen; and

R^3 represents fluoro, chloro, bromo or trifluoromethyl;

R^4 represents hydrogen or fluoro; and

R^5 represents hydrogen or fluoro; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen.

In a yet more preferred embodiment

X represents 1*H*-tetrazol-5-yl;

R^1 represents bromo; or R^1 represents phenyl substituted with methyl, fluoro, chloro, trifluoromethyl, *N,N*-dialkyl-amino-carbonyl or piperidin-1-yl-carbonyl;

R^2 represents hydrogen;

R^3 represents fluoro, chloro, bromo or trifluoromethyl;

R^4 represents hydrogen or fluoro; and

R^5 represents hydrogen.

In most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(2-Trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Trifluoromethyl-phenyl)-*N'*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N'*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N'*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Trifluoromethyl-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-(piperidin-1-yl-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(2-Trifluoromethyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

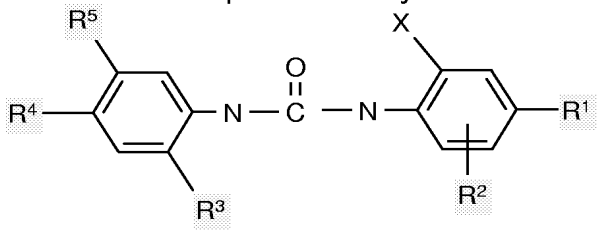
N-(1-Naphthyl)-*N´*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(1-Naphthyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea; or

N-2,3,4-Trifluorophenyl-N´-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

or a pharmaceutically acceptable salt thereof.

In a sixth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula III or III'



(III)

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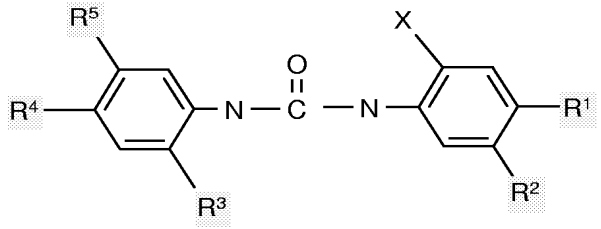


(III')

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined above, and

R^3 represents hydrogen, alkyl, halo (in particular fluoro or chloro), haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo (in particular fluoro or chloro), haloalkyl, nitro, alkoxy (in particular methoxy), phenyl or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo (in particular fluoro), haloalkyl (in particular trifluoromethyl) or nitro.

In a preferred embodiment

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-yl-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, chloro, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo, haloalkyl or nitro.

In a more preferred embodiment

X represents a tetrazolyl group;

R^1 represents hydrogen or halo; or R^1 represents phenyl substituted with haloalkyl or *N,N*-dialkyl-amino-carbonyl;

R^2 represents hydrogen or halo;

R^3 represents hydrogen or halo;

R^4 represents hydrogen, halo, alkoxy or phenyl; and

R^5 represents hydrogen, halo, haloalkyl or nitro.

In an even more preferred embodiment

X represents 1*H*-tetrazol-5-yl;

R^1 represents hydrogen or bromo; or R^1 represents phenyl substituted with trilfuoromethyl or *N,N*-dimethyl-amino-carbonyl;

R^2 represents hydrogen or chloro;

R^3 represents hydrogen, fluoro or chloro;

R^4 represents hydrogen, fluoro, chloro, methoxy or phenyl; and

R^5 represents hydrogen, fluoro, trilfuoromethyl or nitro.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(2-Chloro-4-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(4-Biphenyl)-*N´*-(2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(4-Biphenyl)-*N´*-(5-chloro-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(4-Chloro-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

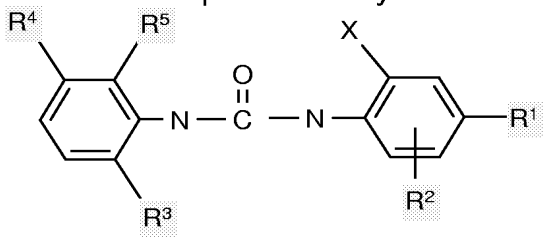
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(4-Methoxyphenyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea; or

N-2,4,5-Trifluorophenyl-N´-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

or a pharmaceutically acceptable salt thereof.

In a seventh preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula IV or IV'



(IV)

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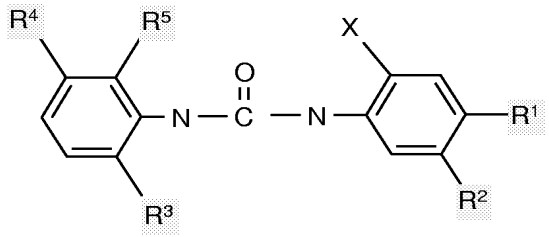


(IV')

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined above, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo or haloalkyl.

In a preferred embodiment

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-

amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; and

R^5 represents hydrogen.

In a more preferred embodiment

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino or *N*-benzoyl-amino;

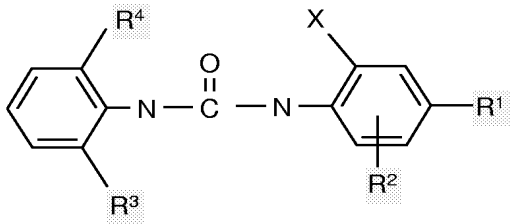
R^2 represents hydrogen, halo, haloalkyl or nitro;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy or alkoxy;

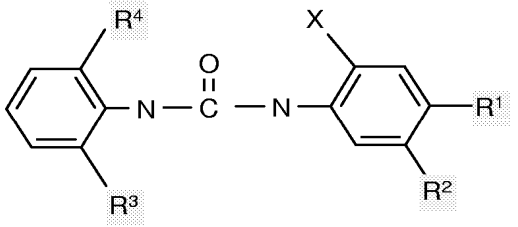
R^4 represents hydrogen, halo, haloalkyl or nitro; and

R^5 represents hydrogen.

In an eight preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula V or V'



(V)



(V')

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined above, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl or pyridyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl or pyridyl.

In a preferred embodiment

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

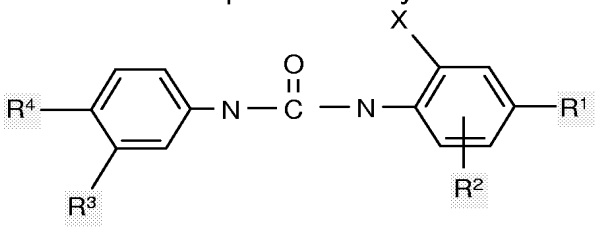
R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl; and

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl.

In a ninth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VI or VI'



(VI)

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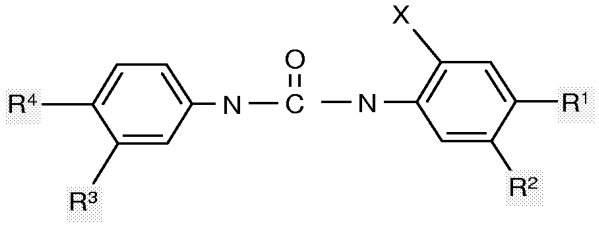


(VI')

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined above, and

R^3 represents hydrogen, alkyl, halo (in particular fluoro or chloro), haloalkyl (in particular trifluoromethyl), nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo (in particular fluoro or chloro), haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group.

In a preferred embodiment

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, *N,N*-dialkyl-amino-carbonyl-alkenyl, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N*-alkyl-(amino-acetic acid)-carbonyl, piperidine-1-carbonyl, piperidinyl-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl;

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group.

In a more preferred embodiment

X represents a tetrazolyl group;

R^1 represents halo or *N,N*-dialkyl-amino-carbonyl-alkenyl; or R^1 represents phenyl substituted with halo, haloalkyl, *N*-alkyl-(amino-acetic acid)-carbonyl, piperidinyl-carbonyl or *N,N*-dialkyl-sulfamoyl;

R^2 represents hydrogen or halo;

R^3 represents halo, haloalkyl; and

R^4 represents halo; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group.

In an even more preferred embodiment

X represents 1*H*-tetrazol-5-yl;

R^1 represents fluoro, chloro, bromo, *N,N*-dimethyl acryl-amide; or phenyl substituted with fluoro, chloro, trifluoromethyl, *N*-methyl-(amino-acetic acid)-carbonyl, piperidinyl-carbonyl or *N,N*-dimethyl-sulfamoyl;

R^2 represents hydrogen, bromo or chloro;

R^3 represents fluoro, chloro or trifluoromethyl; and

R^4 represents fluoro or chloro; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-3´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-chloro-phenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[4-(*N´´,N´´*-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[4-fluoro-2-(1*H*-tetrazol-5-yl)-phenyl]-urea;

N-3,4-Difluorophenyl-N´-[4-bromo-2-(1*H*-tetrazol-5yl)phenyl] urea;

N-(3,4-Dichloro-phenyl)-N´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

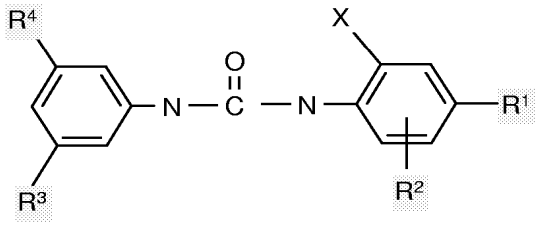
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-N´-[4-chloro-2-(1*H*-tetrazol-5-yl)-phenyl] urea; or

N-(2-Naphthyl)-*N´*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

or a pharmaceutically acceptable salt thereof.

In a tenth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VII or VII'



(VII)

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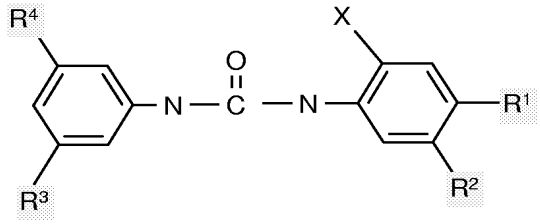


(VII')

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined above, and

R^3 represents hydrogen, alkyl, halo (in particular fluoro or bromo), haloalkyl (in particular trifluoromethyl), haloalkoxy, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo (in particular fluoro), haloalkyl (in particular trifluoromethyl), nitro, alkoxy or phenyl; or phenyl substituted with haloalkyl.

In a preferred embodiment

R^1 represents hydrogen, alkyl (in particular methyl), halo (in particular fluoro, chloro or bromo), hydroxy, alkoxy (in particular methoxy), nitro, amino, *N*-phenyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl (in particular methoxy-carbonyl), phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo (in particular fluoro, chloro or bromo), haloalkyl (in particular trifluoromethyl), haloalkoxy (in particular trifluoromethoxy), nitro, carboxy, alkoxy (in particular methoxy), alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-yl-carbonyl, 4-alkyl-piperazine-1-yl-carbonyl, *N,N*-dialkyl-sulfamoyl, *N,N*-dialkyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl (*N,N*-dimethyl-amino-carbonyl-ethyl), *N,N*-dialkyl-amino-carbonyl-alkenyl (*N,N*-dialkyl acryl-amide), *N*-acetic acid-amino-carbonyl,or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, halo (in particular chloro), alkoxy (in particular methoxy), alkoxy-carbonyl (in particular methoxy-carbonyl), nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl.

In a more preferred embodiment

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo (in particular chloro), hydroxy, alkoxy (in particular methoxy), nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl (in particular methoxy-carbonyl), phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl; and

R^2 represents hydrogen, halo (in particular chloro), alkoxy (in particular methoxy), alkoxy-carbonyl (in particular methoxy-carbonyl), nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl (in particular methyl), halo, haloalkyl (in particular trifluoromethyl), haloalkoxy, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl (in particular methoxy-carbonyl), amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy or phenyl; or phenyl substituted with haloalkyl.

In an even more preferred embodiment

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, *N*-phenyl-amino or alkoxy-carbonyl;

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl or nitro;

R^3 represents alkyl, halo, haloalkyl, nitro, hydroxy, carboxy, alkoxy-carbonyl, amino-carbonyl or benzoyl; and

R^4 represents hydrogen.

In a yet more preferred embodiment

R^1 represents hydrogen, chloro, hydroxy, methoxy, nitro, *N*-phenyl-amino or methoxy-carbonyl;

R^2 represents hydrogen, chloro, methoxy, methoxy-carbonyl or nitro;

R^3 represents methyl, trifluoromethyl, nitro, hydroxy, carboxy, methoxy-carbonyl, amino-carbonyl or benzoyl; and

R^4 represents hydrogen.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxyphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-methoxyphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-methoxcarbonylphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-chlorophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-nitrophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-(phenylamino)phenyl) urea;
N-(3-(Trifluoromethyl)phenyl)-*N'*-(2,4-dihydroxyphenyl) urea;
N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea;
N-(3-(Trifluoromethoxy)phenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-methoxycarbonylphenyl) urea;
N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-nitrophenyl) urea;
N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-methoxyphenyl) urea;
N-(3-Benzoylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-Carbamoylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-Carboxyphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-Hydroxyphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-Methoxycarbonylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-(3-Methylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea; or
N-(3-Nitrophenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;
or a pharmaceutically acceptable salt thereof.

In an eleventh preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VII, wherein
X represents carboxy;
R^1 represents halo (in particular fluoro or bromo), alkyl (in particular methyl) or phenyl;
R^2 represents hydrogen;
R^3 represents haloalkyl (in particular trifluoromethyl); and
R^4 represents hydrogen or haloalkyl (in particular trifluoromethyl).

In a preferred embodiment
X represents carboxy;
R^1 represents fluoro, bromo, methyl or phenyl;
R^2 represents hydrogen;
R^3 represents trifluoromethyl; and
R^4 represents hydrogen or trifluoromethyl.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-bromophenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-chlorophenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-fluorophenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-trifluoromethylphenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-biphenyl) urea; or
N-(3,5-Bis-trifluoromethylphenyl)-*N´*-(2-carboxy-4-biphenyl) urea;

or a pharmaceutically acceptable salt thereof.

In a twelfth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VII, wherein

X represents a tetrazolyl (in particular 1*H*-tetrazol-5-yl) group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo (in particular fluoro, chloro or bromo), hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, *N,N*-dialkyl acryl-amide, 2-*N,N*-dialkyl-carbamoyl-ethyl, alkyl-carbonyl, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo (in particular fluoro, chloro or bromo), haloalkyl (in particular trifluoromethyl), haloalkoxy, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, *N*-acetic acid-amino-carbonyl, *N*-alkyl-*N*-acetic acid-amino-carbonyl, 4-alkyl-piperazine-1-yl-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, halo (in particular chloro or bromo), alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo (in particular fluoro or bromo), haloalkyl (in particular trifluoromethyl), nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl or pyridyl; or

R^3 represents phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo (in particular fluoro), haloalkyl (in particular trifluoromethyl), nitro, alkoxy, phenyl or phenyl substituted with haloalkyl.

In a preferred embodiment

X represents a tetrazolyl (in particular 1*H*-tetrazol-5-yl) group;

R^1 represents hydrogen, halo (in particular fluoro, chloro or bromo), nitro, amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1 represents phenyl substituted with halo (in particular fluoro, chloro or bromo), haloalkyl (in particular trifluoromethyl), nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl; and

R^2 represents hydrogen or halo (in particular chloro or bromo);

R^3 represents halo (in particular fluoro or bromo), haloalkyl (in particular trifluoromethyl), acetyl, phenyl or pyridyl; and

R^4 represents hydrogen, halo (in particular fluoro) or haloalkyl (in particular trifluoromethyl).

In a more preferred embodiment

X represents 1*H*-tetrazol-5-yl;

R^1 represents hydrogen, fluoro, chloro, bromo, nitro, amino, methyl-carbonyl-amino, *N*-benzoyl-amino, phenyl, naphthyl, pyridyl, furyl or thienyl; or R^1

represents phenyl substituted with fluoro, chloro, bromo, trifluoromethyl, nitro, carboxy, methoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dimethyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, 4-methyl-piperazine-1-carbonyl, *N,N*-dimethyl-sulfamoyl or 4-methyl-piperazine-1-sulfonyl;

R^2 represents hydrogen, chloro or bromo;

R^3 represents fluoro, bromo, trifluoromethyl, acetyl, phenyl or pyridyl; and

R^4 represents hydrogen, fluoro or trifluoromethyl.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(3-Trifluoromethylphenyl)-*N'*-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-nitro-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(1-naphthyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(2-naphthyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(3-pyridyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-trifluoromethylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(3-furyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(3-thienyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(3-nitrophenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-ethoxycarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-diethylaminocarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-benzoylamino-phenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-benzoylamino-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-(3-Pyridyl)phenyl)-*N'*-4-bromo-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Bromophenyl)-*N´*-(2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Trifluoromethylphenyl)-*N´*-(2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Trifluoromethylphenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Bromophenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Bromophenyl)-*N´*-(4´-(*N,N*-dimethylcarbamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Trifluromethylphenyl)-*N´*-(4-amino-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Trifluoromethylphenyl)-*N´*-(4-acetylamino-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-aminocarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N´*-(4´-(*N,N*-dimethylcarbamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-carboxyphenyl)-2-(1H-tetrazol-5-yl)phenyl urea;

N-(3-Biphenylyl)-*N´*-(2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-phenylaminocarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Acetylphenyl)-*N'*-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Biphenyl)-*N´*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-(3-Pyridyl)phenyl)-*N´*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Bromophenyl)-*N´*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-benzoylcarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Bromophenyl)-*N´*-[4´-(sulfonamido-*N'*-methylpiperazinium chloride)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;

N-(3-Bromophenyl)-*N´*-[4´-carbamoyl-*N'*-methylpiperazine)-2-(1*H*-tetrazol-5-yl)-4'-biphenyl] urea;

N-(3-Trifluoromethylphenyl)-*N´*-[4-fluoro-2-(1*H*-tetrazol-yl)phenyl] urea;

N-(3-Trifluoromethylphenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3-Trifluoromethylphenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-5-yl]-urea;

N-(3-Bromophenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis(trifluoromethyl)phenyl)-N´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(3,5-Difluorophenyl)-N´-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea; or

N-(3,5-Difluoro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;

or a pharmaceutically acceptable salt thereof.

In a thirteenth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VII, wherein

X represents a tetrazolyl group;

R^1 represents halo (in particular chloro), *N,N*-dialkyl acryl-amide, *N,N*-dialkyl-amino-carbonyl-alkyl, phenyl; or R^1 represents phenyl substituted with halo (in

particular fluoro or chloro), haloalkyl (in particular trifluoromethyl), haloalkoxy (in particular trifluoromethoxy), alkoxy (in particular methoxy), amino-carbonyl, *N,N*-dialkyl-sulfamoyl, *N,N*-dialkyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl (in particular *N,N*-dimethyl-amino-carbonyl-ethyl), *N,N*-dialkyl-amino-carbonyl-alkenyl (in particular *N,N*-dialkyl acryl-amide), *N*-acetic acid-amino-carbonyl, *N*-alkyl-*N*-acetic acid-amino-carbonyl or piperidine-1-yl-carbonyl;

R^2 represents hydrogen;

R^3 represents alkyl, halo (in particular fluoro or chloro) or haloalkyl (in particular trifluoromethyl); and

R^4 represents alkyl, halo (in particular fluoro or chloro) or haloalkyl (in particular trifluoromethyl).

In a preferred embodiment

X represents a tetrazolyl group;

R^1 represents halo (in particular chloro); or R^1 represents phenyl substituted in position 3 or 4 with halo (in particular fluoro or chloro), haloalkyl (in particular trifluoromethyl), haloalkoxy (in particular trifluoromethoxy), alkoxy (in particular methoxy), amino-carbonyl, *N,N*-dialkyl-sulfamoyl, *N,N*-dialkyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl (in particular *N,N*-dialkyl acryl-amide), *N*-acetic acid-amino-carbonyl or piperidine-1-yl-carbonyl;

R^2 represents hydrogen;

R^3 represents halo (in particular fluoro or chloro) or haloalkyl (in particular trifluoromethyl); and

R^4 represents halo (in particular fluoro or chloro) or haloalkyl (in particular trifluoromethyl).

In a more preferred embodiment

X represents 1*H*-tetrazol-5-yl;

R^1 represents chloro; or R^1 represents phenyl substituted in position 3 or 4 with fluoro, chloro, trifluoromethyl, trifluoromethoxy, methoxy, amino-carbonyl, *N,N*-dimethyl-sulfamoyl, *N,N*-dimethyl-amino-carbonyl, *N,N*-dimethyl-amino-carbonyl-ethyl, *N,N*-dialkyl acryl-amide, *N*-acetic acid-amino-carbonyl or piperidine-1-carbonyl;

R^2 represents hydrogen;

R^3 represents fluoro, chloro or trifluoromethyl; and

R^4 represents fluoro, chloro or trifluoromethyl.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(3,5-Difluorophenyl)-*N'*-[4'-chloro-2-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(3,5-Dichlorophenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Difluorophenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Dichlorophenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Difluorophenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Dichlorophenyl)-*N*´-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Difluorophenyl)-*N*´-[4´-fluoro-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Dichlorophenyl)-*N*´-[4´-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Difluorophenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethoxy-biphenyl-4-yl]-urea;

N-(3,5-Dichlorophenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethoxy-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-4´-trifluoro-methoxy-biphenyl-4-yl]-urea;

N-(3,5-Dichlorophenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-3´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-[3-(1*H*-tetrazol-5-yl)-3´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Difluorophenyl)-*N*´-[4´-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-[4´-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3,5-Difluorophenyl)-*N*´-(4´-carbamoyl-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Dichlorophenyl)-*N*´-(4´-(*N,N*-dimethylcarbamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N*´-(4´-carbamoyl-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Dichlorophenyl)-*N*´-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Difluorophenyl)-*N*´-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N'*-4-(4-piperidine-1-yl-carbonyl-phenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Difluorophenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N´´,N´´*-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Dichloro-phenyl)-*N'*-[2-(*1H*-tetrazol-5-yl)-4-(2-*N,N*-dimethyl-carbamoyl-ethyl)-phenyl] urea; or

N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[2-(*1H*-tetrazol-5-yl)-4-(2-*N,N*-dimethyl-carbamoyl-ethyl)-phenyl] urea;

or a pharmaceutically acceptable salt thereof.

In a fourteenth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VII, wherein

X represents an oxadiazolyl group;

R^1 represents hydrogen;

R^2 represents hydrogen;

R^3 represents haloalkyl (in particular trifluoromethyl); and

R^4 represents hydrogen.

In a preferred embodiment

X represents 2-oxo-3*H*-1,3,4-oxadiazol-5-yl;

R^1 represents hydrogen;

R^2 represents hydrogen;

R^3 represents trifluoromethyl; and

R^4 represents hydrogen.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(3-Trifluoromethylphenyl)-*N'*-2-(2-oxo-3*H*-1,3,4-oxadiazol-5-yl)phenyl urea;

or a pharmaceutically acceptable salt thereof.

In a fifteenth preferred embodiment the diphenyl urea derivative for use according to the invention is represented by Formula VII, wherein

X represents 1,2,3-triazolyl or 1,2,4-triazolyl;

R^1 represents hydrogen or phenyl;

R^2 represents hydrogen;

R^3 represents haloalkyl; and

R^4 represents hydrogen.

In a more preferred embodiment

X represents 4-hydroxy-1,2,4-triazol-3-yl or 3-oxo-1,2-dihydro-1,2,4-triazol-1-yl;

R^1 represents hydrogen or phenyl;

R^2 represents hydrogen;

R^3 represents trifluoromethyl; and

R^4 represents hydrogen.

In a most preferred embodiment the diphenyl urea derivative for use according to the invention is

N-(3-Trifluoromethylphenyl)-*N'*-2-(4-hydroxy-1,2,4-triazol-3-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N'*-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl urea; or

N-(3-Trifluoromethylphenyl)-*N'*-4-biphenylyl-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl urea;

or a pharmaceutically acceptable salt thereof.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo, and haloalkyl, haloalkoxy and halophenyl groups designate alkyl, alkoxy and phenyl groups as defined herein, which alkyl, alkoxy or phenyl group is substituted one or more times with halo. Thus a trihalomethyl group represents e.g. a trifluoromethyl group, a trichloromethyl group, and similar trihalo-substituted alkyl groups, and a trihaloalkoxy group designates e.g. a trifluoromethoxy group, a trichloromethoxy, and similar trihalosubstituted alkoxy groups. Preferred haloalkyl groups of the invention include trihalogenmethyl, preferably $-CF_3$, and preferred trihaloalkoxy groups of the invention include trihalomethoxy, preferably $-OCF_3$.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

Pharmaceutically Acceptable Salts

The diphenyl urea derivative for use according to the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a diphenyl urea derivative for use according to the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of the diphenyl urea derivative for use according to the invention include, without limitation, the sodium, the

potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of the diphenyl urea derivative for use according to the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

The diphenyl urea derivative for use according to the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Cardiac Diseases

The present invention relates to the use of ERG channel opening compounds for the treatment, prevention or alleviation of an abnormal rhythm of the heart.

In a more specific embodiment the disease, disorder or condition contemplated according to the invention is a cardiac arrhytmia.

In an even more specific embodiment the cardiac disease, disorder or condition of the invention is cardiac arrhytmia, atrial arrhythmia, ventricular arrhythmia, atrial fibrillation, ventricular fibrillation, tachyarrhythmia, atrial tachyarrhythmia, ventricular tachyarrhythmia, bradyarrhythmias, or any other abnormal rhythm, e.g. caused by myocardial ischaemia, myocardial infarction, cardiac hypertrophy, cardiomyopathy or a genetic disease.

In a yet more preferred embodiment a cardiac disease, disorder or condition of the invention is cardiac arrhythmia, atrial fibrillation and/or ventricular tachyarrhythmia.

In a most preferred embodiment a cardiac disease, disorder or condition of the invention is cardiac arrhythmia.

Methods of Preparation

The diphenyl urea derivative for use according to the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in publications referenced above. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one diphenyl urea derivative for use according to the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the diphenyl urea derivative for use according to the invention.

While the diphenyl urea derivative for use according to the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the diphenyl urea derivative for use according to the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the diphenyl urea derivative for use according to the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

Alternatively, or concurrently, administration may be by the oral or nasal route or directly to the lungs. In a preferred embodiment, the compounds of this invention may be administered by inhalation. For inhalation therapy the compound may be in a solution useful for administration by liquid aerosol, metered dose inhalers, or in a form suitable for a dry powder inhaler. The dosage administered will be dependent

upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In a preferred embodiment, the diphenyl urea derivative for use according to the invention may be formulated as aerosols. The formulation of pharmaceutical aerosols is routine to those skilled in the art, see e.g. Sciarra J, in Remington: The Science and Practice of Pharmacy 19TH Edition, 1995, Chapter 95, Mack Publishing Company, Easton. The diphenyl urea derivative for use according to the invention may be formulated as solution aerosols, dispersion or suspension aerosols of dry powders, emulsions or colloid preparations. The aerosol may be delivered using any propellant system known to those skilled in the art. The aerosols may be applied to the upper respiratory tract, for example by nasal inhalation, or to the lower respiratory tract or to both.

In other preferred embodiments of the invention, the diphenyl urea derivative for use according to the invention may be formulated into particulates or micronized to improve bioavailability and digestive absorption. In particular, talniflumate may be formulated and micronized using standard techniques in the art, including the methods discussed by Chaumeil J C, *et al.*, Methods Find. Exp. Clin. Pharmacol. 1998 20 3 211-215. In this process, grinding may be carried out in ball or hammer mills of the customary type. These procedures can also be carried out by micronization in gaseous jet micronizers which have the advantage of not heating the substances to be micronized.

The devices of the present invention may be any device adapted to introduce one or more therapeutic compositions into the upper and/or lower respiratory tract. In some preferred embodiments, the devices of the present invention may be metered- dose inhalers. The devices may be adapted to deliver the therapeutic compositions of the invention in the form of a finely dispersed mist of liquid, foam or powder. The devices may use any propellant system known to those in the art including, but not limited to, pumps, liquefied-gas, compressed gas and the like. Devices of the present invention typically comprise a container with one or more valves throw which the flow of the therapeutic composition travels and an actuator for controlling the flow. Suitable devices for use in the present invention may be seen in, for example, in Remington: The Science and Practice of Pharmacy, *op cit*.

The diphenyl urea derivative for use according to the invention can be provided alone, or in combination with other agents that modulate a particular pathological process. For example, an agent of the present invention can be administered in combination with anti-asthma agents. In another embodiment, the diphenyl urea derivative for use according to the invention may be administered in combination with expectorants, mucolytics, antibiotics, antihistamines or decongestants. In still another embodiment, the diphenyl urea derivative for use

according to the invention may be administered along with a surfactant, a stabilizing agent, an absorption-enhancing agent, a beta adrenoreceptor or purine receptor agonist or a flavoring or other agent that increases the palatability of the compositions. As an example, compositions of the invention may contain, in addition to the active substance, an expectorant such as guaifenesin, a stabilizing agent such as cyclodextran and/or an absorption-enhancing agent such as chitosan. Any such agents may be used in the compositions of the invention.

As used herein, two or more active ingredients are said to be administered in combination when the agents are administered simultaneously or are administered independently in a fashion such that the agents will act at the same time.

The diphenyl urea derivative for use according to the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The diphenyl urea derivative for use according to the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either the diphenyl urea derivative for use according to the invention or a pharmaceutically acceptable salt of such compounds.

For preparing pharmaceutical compositions from the diphenyl urea derivative for use according to the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The diphenyl urea derivative for use according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the diphenyl urea derivative for use according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method of treatment, prevention or alleviation of a cardiac disease, disorder or condition of a living animal body, including a human, which disorder, disease or condition is responsive to activation of an ERG channel, in particular the human ERG1 channel (Human Ether-a-go-go Related Gene channel, HERG1 channel), which method comprises the step of

administering to such a living animal body in need thereof, a therapeutically effective amount a compound capable of activating the ERG channel, or a pharmaceutically-acceptable addition salt thereof.

In a preferred embodiment the cardiac disease, disorder or condition is cardiac arrhythmia, atrial arrhythmia, ventricular arrhythmia, atrial fibrillation, ventricular fibrillation, tachyarrhythmia, atrial tachyarrhythmia, ventricular tachyarrhythmia, bradyarrhythmias, or any other abnormal rhythm, e.g. caused by myocardial ischaemia, myocardial infarction, cardiac hypertrophy, cardiomyopathy or a genetic disease.

In a most preferred embodiment a cardiac disease, disorder or condition of the invention is cardiac arrhythmia.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 1 to about 500 mg API per day, most preferred of from about 1 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

Expression and Functional Characterization of the HERG1 Channel in Mammalian Cells

In this example the HERG1 channel opening activity of the compounds for use according to the invention was determined using mammalian HEK293 cells stably expressing HERG1 channels. The compounds representative for use according to the invention are

N-(2-Chloro-4-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea (Compound A);

N-(3,5-Bis(trifluoromethyl)phenyl)-N´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)phenyl] urea (Compound B); and

N-(4-Fluoro-3-trifluoromethyl-phenyl)-N´-[4-chloro-2-(1*H*-tetrazol-5-yl)-phenyl] urea (Compound C).

Cloning and Expression

The HERG1 channel is expressed in oocytes from *Xenopus laevis*. The gene encoding the HERG1 channel was cloned as described by *Warmke & Ganetzky*; Proc. Natl. Acad. Sci. USA 1994 91 3438-3442.

To ensure functional expression in oocytes, the HERG1 gene was sub-cloned in the shuttle-vector pXOOM as described by *Jespersen et al.*; Biotechniques 2002 32 536-540.

Electrophysiological Determination

The electrical current through the HERG1 channel is measured using conventional two-electrode voltage clamp technology. HERG1 current is activated by a voltage step protocol. Briefly this protocol goes from +20 mV for 1 seconds followed by tail current recording for 3 s at -60 mV. Between the steps, cells are clamped to -80 mV for 3 seconds to ensure complete release of inactivation for the HERG channels.

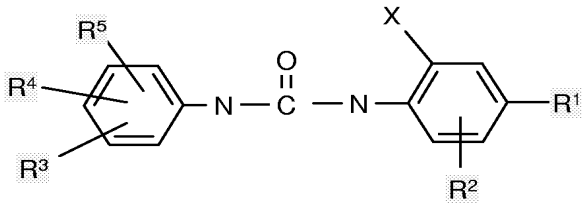
Results

The Oocytes stably expressing HERG1 channels were challenged by a step protocol as described above. Having reached a stable current level the compound representative for use according to the invention was added (i.e. *N*-(3,5-Bis(trifluoromethyl)phenyl)-N´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)phenyl] urea), and a substantial increase in the tail current was observed.

Control currents in the absence of test compound were also generated and the results of these experiments are presented in Figs. 1-3, from which figures it appears that the compounds for use according to the invention are in fact HERG activators (openers).

CLAIMS:

1. The use of a diphenyl urea derivative represented by Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

X represents hydroxy, carboxy, a tetrazolyl group, or an oxadiazolyl or a triazolyl group, which oxadiazolyl a triazolyl groups may optionally be substituted with oxo and/or hydroxy groups;

R^1 represents hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, sulfamoyl, *N,N*-dialkylsulfamoyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted once or twice with alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, nitro, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, piperazinyl-carbonyl, alkyl-piperazinyl-carbonyl, amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, sulfamoyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl;

R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, haloalkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl, pyridyl, or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo, haloalkyl or nitro; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen;

for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of an abnormal heart rhythm.

2. The use according to claim 1, wherein X represents hydroxy, carboxy, a tetrazolyl group, or an oxadiazolyl or a triazolyl group, which oxadiazolyl a triazolyl groups may optionally be substituted with oxo or hydroxy groups.

3. The use according to claim 2, wherein X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group.

4. The use according to any one of claims 1-3, wherein

R^1 represents hydrogen, alkyl, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with alkyl, halo, haloalkyl, alkoxy, haloalkoxy, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, alkyl-piperazinyl-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl.

5. The use according to claim 4, wherein

R^1 represents hydrogen, alkyl, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, alkoxy-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with alkyl, halo, haloalkyl, alkoxy, haloalkoxy, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl, *N*-alkyl-(amino-acetic acid)-carbonyl, *N*-acetic acid-amino-carbonyl, piperidinyl-carbonyl, alkyl-piperazinyl-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N,N*-dialkyl-sulfamoyl or alkyl-piperazinyl-sulfonyl.

6. The use according to any one of claims 1-5, wherein

R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl.

7. The use according to any one of claims 1-6, wherein

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, haloalkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

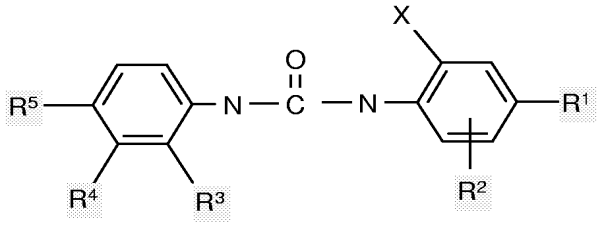
R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl, pyridyl, or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo, haloalkyl or nitro; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen.

8. The use according to any one of claims 1-7, wherein the diphenyl urea derivative is represented by Formula II



(II)

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined in claim 1, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, or phenyl; or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo or haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen.

9. The use according to claim 8, wherein

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with alkyl, halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidin-1-yl-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, alkyl-piperazinyl-carbonyl, *N,N*-dialkylsulfamoyl or alkyl-piperazinyl-sulfonyl;

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl; and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen; alkyl; halo; haloalkyl; nitro; alkoxy; phenyl or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo or haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group; and

R^5 represents hydrogen.

10. The use according to claim 9, wherein the diphenyl urea derivative is

N-(2-Trifluoromethyl-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Trifluoromethyl-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Fluoro-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Bromo-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Trifluoromethyl-phenyl)-*N´*-[4´-methyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(2-Chloro-phenyl)-*N´*-[4´-(piperidin-1-yl-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(2-Trifluoromethyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

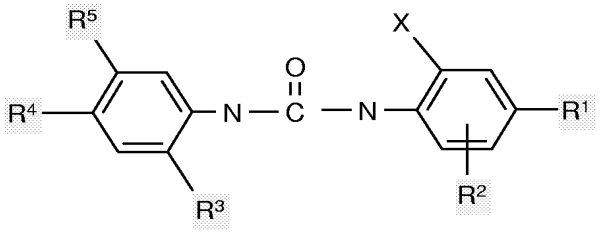
N-(1-Naphthyl)-*N´*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(1-Naphthyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea; or

N-2,3,4-Trifluorophenyl-N´-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

or a pharmaceutically acceptable salt thereof.

11. The use according to any one of claims 1-7, wherein the diphenyl urea derivative is represented by Formula III



(III)

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined in claim 1, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo, haloalkyl or nitro.

12. The use according to claim 11, wherein

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-yl-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, chloro, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo, haloalkyl or nitro.

13. The use according to claim 12, wherein the diphenyl urea derivative is

N-(2-Chloro-4-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(4-Biphenyl)-*N´*-(2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(4-Biphenyl)-*N´*-(5-chloro-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(4-Chloro-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

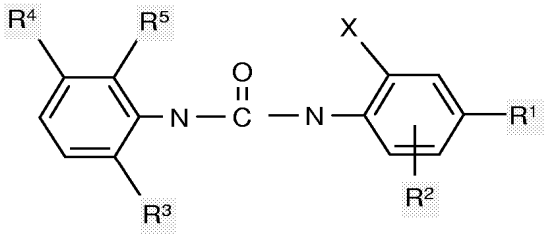
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(4-Methoxyphenyl)-*N´*-[4´-(*N´´,N´´*-dimethyl-amino-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea; or

N-2,4,5-Trifluorophenyl-N´-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

or a pharmaceutically acceptable salt thereof.

14. The use according to any one of claims 1-7, wherein the diphenyl urea derivative is represented by Formula IV



(IV)

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined in claim 1, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; and

R^5 represents hydrogen, halo or haloalkyl.

15. The use according to claim 14, wherein

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, halo, haloalkyl, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl;

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; and

R^5 represents hydrogen.

16. The use according to claim 15, wherein

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino or *N*-benzoyl-amino;

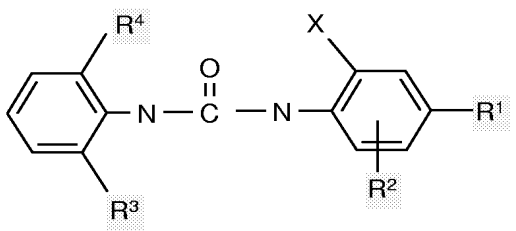
R^2 represents hydrogen, halo, haloalkyl or nitro;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy or alkoxy;

R^4 represents hydrogen, halo, haloalkyl or nitro; and

R^5 represents hydrogen.

17. The use according to any one of claims 1-7, wherein the diphenyl urea derivative is represented by Formula V



(V)

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined in claim 1, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl or pyridyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, phenyl or pyridyl.

18. The use according to claim 17, wherein

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

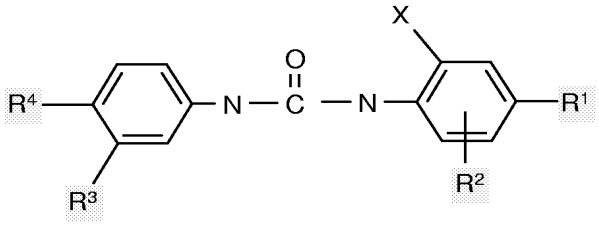
R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl; and

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl.

19. The use according to any one of claims 1-7, wherein the diphenyl urea derivative is represented by Formula VI



(VI)

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined in claim 1, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group.

20. The use according to claim 19, wherein

X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, *N,N*-dialkyl-amino-carbonyl-alkenyl, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N*-alkyl-(amino-acetic acid)-carbonyl, piperidine-1-carbonyl, piperidinyl-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl;

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl; and

R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl; or phenyl substituted with haloalkyl; or

R^3 and R^4 together with the phenyl to which they are attached form a naphthyl group.

21. The use according to claim 20, wherein the diphenyl urea derivative is

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-3´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(4-Fluoro-3-chloro-phenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N´*-[4-(*N´´,N´´*-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[4´-(piperidine-1-carbonyl)-3-(*1H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N´*-[4-fluoro-2-(1*H*-tetrazol-5-yl)-phenyl]-urea;

N-3,4-Difluorophenyl-N´-[4-bromo-2-(1*H*-tetrazol-5yl)phenyl] urea;

N-(3,4-Dichloro-phenyl)-N´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

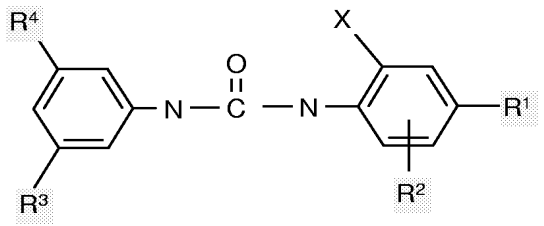
N-(4-Chloro-3-trifluoromethyl-phenyl)-N´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(4-Fluoro-3-trifluoromethyl-phenyl)-N´-[4-chloro-2-(1*H*-tetrazol-5-yl)-phenyl] urea; or

N-(2-Naphthyl)-*N´*-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea;

or a pharmaceutically acceptable salt thereof.

22. The use according to any one of claims 1-7, wherein the diphenyl urea derivative is represented by Formula VII



(VII)

or a pharmaceutically acceptable salt thereof, wherein

X, R^1 and R^2 are as defined in claim 1, and

R^3 represents hydrogen, alkyl, halo, haloalkyl, haloalkoxy, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy or phenyl; or phenyl substituted with haloalkyl.

23. The use according to claim 22, wherein

R^1 represents hydrogen, alkyl, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with halo, haloalkyl, haloalkoxy, nitro, carboxy, alkoxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-yl-carbonyl, 4-alkyl-piperazine-1-yl-carbonyl, *N,N*-dialkyl-sulfamoyl, *N,N*-dialkyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N*-acetic acid-amino-carbonyl,or 4-alkyl-piperazine-1-yl-sulfonyl; and

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl.

24. The use according to claim 23, wherein

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, *N*-benzoyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or

R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, amino-carbonyl-*N*-alkyl-piperazine, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl; and

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;

R^3 represents hydrogen, alkyl, halo, haloalkyl, haloalkoxy, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl, or pyridyl; or phenyl substituted with alkyl, halo or haloalkyl; and

R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy or phenyl; or phenyl substituted with haloalkyl.

25. The use according to claim 24, wherein

X represents hydroxy or carboxy;

R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, *N*-phenyl-amino or alkoxy-carbonyl;

R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl or nitro;

R^3 represents alkyl, halo, haloalkyl, nitro, hydroxy, carboxy, alkoxy-carbonyl, amino-carbonyl or benzoyl; and

R^4 represents hydrogen.

26. The use according to claim 25, wherein the diphenyl urea derivative is

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxyphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-methoxyphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-methoxcarbonylphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-chlorophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-nitrophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-(phenylamino)phenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2,4-dihydroxyphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea;

N-(3-(Trifluoromethoxy)phenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-methoxycarbonylphenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-nitrophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-(Trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-methoxyphenyl) urea;

N-(3-Benzoylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-Carbamoylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-Carboxyphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-Hydroxyphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-Methoxycarbonylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-(3-Methylphenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea; or

N-(3-Nitrophenyl)-*N'*-(2-hydroxy-5-chlorophenyl) urea;

or a pharmaceutically acceptable salt thereof.

27. The use according to claim 22, wherein

X represents carboxy;

R^1 represents halo, alkyl or phenyl;

R^2 represents hydrogen;

R^3 represents haloalkyl; and

R^4 represents hydrogen or haloalkyl.

28. The use according to claim 27, wherein the diphenyl urea derivative is
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-bromophenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-chlorophenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-fluorophenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-trifluoromethylphenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-carboxy-4-biphenyl) urea; or
N-(3,5-Bis-trifluoromethylphenyl)-*N´*-(2-carboxy-4-biphenyl) urea;
or a pharmaceutically acceptable salt thereof.

29. The use according to claim 22, wherein
X represents a tetrazolyl group, an oxadiazolyl group or a triazolyl group;
R^1 represents hydrogen, halo, hydroxy, alkoxy, nitro, amino, *N*-phenyl-amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, *N,N*-dialkyl acryl-amide, 2-*N,N*-dialkyl-carbamoyl-ethyl, alkyl-carbonyl, alkoxy-carbonyl, phenyl, naphthyl, pyridyl, furyl or thienyl; or
R^1 represents phenyl substituted with halo, haloalkyl, haloalkoxy, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, piperidine-1-carbonyl, *N*-acetic acid-amino-carbonyl, *N*-alkyl-*N*-acetic acid-amino-carbonyl, 4-alkyl-piperazine-1-yl-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-yl-sulfonyl; and
R^2 represents hydrogen, halo, alkoxy, alkoxy-carbonyl, nitro, halophenyl, haloalkyl-phenyl or haloalkoxy-phenyl;
R^3 represents hydrogen, alkyl, halo, haloalkyl, nitro, hydroxy, alkoxy, carboxy, alkyl-carbonyl, alkoxy-carbonyl, amino-carbonyl, benzoyl, acetyl, phenyl or pyridyl; or
R^3 represents phenyl substituted with alkyl, halo or haloalkyl; and
R^4 represents hydrogen, alkyl, halo, haloalkyl, nitro, alkoxy, phenyl or phenyl substituted with haloalkyl.

30. The use according to claim 29, wherein
X represents a tetrazolyl group;
R^1 represents hydrogen, halo, nitro, amino, alkyl-carbonyl-amino, *N*-benzoyl-amino, phenyl, naphthyl, pyridyl, furyl or thienyl; or
R^1 represents phenyl substituted with halo, haloalkyl, nitro, carboxy, alkoxy-carbonyl, amino-carbonyl (carbamoyl), *N,N*-dialkyl-amino-carbonyl, *N*-phenyl-amino-carbonyl, 4-alkyl-piperazine-1-carbonyl, *N,N*-dialkyl-sulfamoyl or 4-alkyl-piperazine-1-sulfonyl; and
R^2 represents hydrogen or halo;
R^3 represents halo, haloalkyl, acetyl, phenyl or pyridyl; and

R^4 represents hydrogen, halo or haloalkyl.

31. The use according to claim 30, wherein the diphenyl urea derivative is
N-(3-Trifluoromethylphenyl)-*N'*-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-nitro-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(1-naphthyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(2-naphthyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(3-pyridyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(4-trifluoromethylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(3-furyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(3-thienyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(3-nitrophenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(4-ethoxycarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(4-diethylaminocarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(4-benzoylamino-phenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-benzoylamino-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-(3-Pyridyl)phenyl)-*N'*-4-bromo-2-(1*H*-tetrazol-5-yl)phenyl urea;
N-(3-Bromophenyl)-*N´*-(2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;
N-(3-Bromophenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;
N-(3-Bromophenyl)-*N´*-(4´-(*N,N*-dimethylcarbamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;
N-(3-Trifluromethylphenyl)-*N´*-(4-amino-2-(1*H*-tetrazol-5-yl)phenyl) urea;
N-(3-Trifluoromethylphenyl)-*N´*-(4-acetylamino-2-(1*H*-tetrazol-5-yl)phenyl) urea;
N-(3-Trifluoromethylphenyl)-*N'*-4-(4-aminocarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Trifluoromethylphenyl)-*N´*-(4´-(*N,N*-dimethylcarbamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-carboxyphenyl)-2-(1H-tetrazol-5-yl)phenyl urea;

N-(3-Biphenylyl)-*N´*-(2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-phenylaminocarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Acetylphenyl)-*N'*-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Biphenyl)-*N´*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-(3-Pyridyl)phenyl)-*N´*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Bromophenyl)-*N´*-(4-bromo-2-(1*H*-tetrazol-5-yl)phenyl) urea;

N-(3-Trifluoromethylphenyl)-*N'*-4-(4-benzoylcarbonylphenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3-Bromophenyl)-*N´*-[4´-(sulfonamido-*N'*-methylpiperazinium chloride)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;

N-(3-Bromophenyl)-*N´*-[4´-carbamoyl-*N'*-methylpiperazine)-2-(1*H*-tetrazol-5-yl)-4'-biphenyl] urea;

N-(3-Trifluoromethylphenyl)-*N´*-[4-fluoro-2-(1*H*-tetrazol-yl)phenyl] urea;

N-(3-Trifluoromethylphenyl)-*N´*-[4´-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;

N-(3-Trifluoromethylphenyl)-*N´*-[4´-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-5-yl]-urea;

N-(3-Bromophenyl)-*N´*-[3-(1*H*-tetrazol-5-yl)-4´-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis(trifluoromethyl)phenyl)-N´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)phenyl] urea;

N-(3,5-Difluorophenyl)-N´-[4-bromo-2-(1*H*-tetrazol-5-yl)phenyl] urea; or

N-(3,5-Difluoro-phenyl)-N´-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;

or a pharmaceutically acceptable salt thereof.

32. The use according to claim 29, wherein

X represents a tetrazolyl group;

R^1 represents halo, *N,N*-dialkyl acryl-amide, *N,N*-dialkyl-amino-carbonyl-alkyl, phenyl; or

R^1 represents phenyl substituted with halo, haloalkyl, haloalkoxy, alkoxy, amino-carbonyl, *N,N*-dialkyl-sulfamoyl, *N,N*-dialkyl-amino-carbonyl, *N,N*-dialkyl-amino-carbonyl-alkyl, *N,N*-dialkyl-amino-carbonyl-alkenyl, *N*-acetic acid-amino-carbonyl, *N*-alkyl-*N*-acetic acid-amino-carbonyl or piperidine-1-yl-carbonyl; and

R^2 represents hydrogen;

R^3 represents alkyl, halo or haloalkyl; and
R^4 represents alkyl, halo or haloalkyl.

33. The use according to claim 32, wherein the diphenyl urea derivative is
N-(3,5-Difluorophenyl)-*N'*-[4'-chloro-2-(1*H*-tetrazol-5-yl)phenyl] urea;
N-(3,5-Dichlorophenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluorophenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichlorophenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Difluorophenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Dichlorophenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluorophenyl)-*N'*-[4'-fluoro-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[4'-chloro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[4'-fluoro-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Dichlorophenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluorophenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Dichlorophenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoromethoxy-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-4'-trifluoro-methoxy-biphenyl-4-yl]-urea;
N-(3,5-Dichlorophenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea;
N-(3,5-Difluorophenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[4'-methoxy-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-urea;
N-(3,5-Difluorophenyl)-*N'*-(4'-carbamoyl-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;
N-(3,5-Dichlorophenyl)-*N'*-(4'-(*N,N*-dimethylcarbamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N´*-(4´-carbamoyl-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Dichlorophenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Difluorophenyl)-*N´*-(4´-(*N,N*-dimethylsulfamoyl)-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea;

N-(3,5-Bis-trifluoromethylphenyl)-*N'*-4-(4-piperidine-1-yl-carbonyl-phenyl)-2-(1*H*-tetrazol-5-yl)phenyl urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Difluorophenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N´-{4´-[carbonyl-(N´´-methyl)-amino-acetic acid]-2-(*1H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Dichloro-phenyl)-*N´*-[4-(*N´´,N´´*-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Dichloro-phenyl)-*N'*-[2-(*1H*-tetrazol-5-yl)-4-(2-*N,N*-dimethyl-carbamoyl-ethyl)-phenyl] urea; or

N-(3,5-Bis-trifluoromethylphenyl)-*N'*-[2-(*1H*-tetrazol-5-yl)-4-(2-*N,N*-dimethyl-carbamoyl-ethyl)-phenyl] urea;

or a pharmaceutically acceptable salt thereof.

34. The use according to claim 29, wherein

X represents an oxadiazolyl group;

R^1 represents hydrogen;

R^2 represents hydrogen;

R^3 represents haloalkyl; and

R^4 represents hydrogen.

35. The use according to claim 34, wherein the diphenyl urea derivative is

N-(3-Trifluoromethylphenyl)-*N'*-2-(2-oxo-3*H*-1,3,4-oxadiazol-5-yl)phenyl urea;

or a pharmaceutically acceptable salt thereof.

36. The use according to claim 29, wherein

X represents 1,2,3-triazolyl or 1,2,4-triazolyl;

R^1 represents hydrogen or phenyl;

R^2 represents hydrogen;

R^3 represents haloalkyl; and

R^4 represents hydrogen.

37. The use according to claim 36, wherein the diphenyl urea derivative is *N*-(3-Trifluoromethylphenyl)-*N'*-2-(4-hydroxy-1,2,4-triazol-3-yl)phenyl urea; *N*-(3-Trifluoromethylphenyl)-*N'*-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl urea; or

N-(3-Trifluoromethylphenyl)-*N'*-4-biphenylyl-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl urea;

or a pharmaceutically acceptable salt thereof.

38. The use according to any one of claims 1-37, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a cardiac arrhytmia.

39. The use according to claim 38, wherein the cardiac arrhytmia is cardiac arrhythmia, atrial arrhythmia, ventricular arrhythmia, atrial fibrillation, ventricular fibrillation, tachyarrhythmia, atrial tachyarrhythmia, ventricular tachyarrhythmia or bradyarrhythmias.

40. The use according to claim 39, wherein the cardiac arrhytmia is cardiac arrhythmia, atrial fibrillation and/or ventricular tachyarrhythmia.

41. A method of treatment, prevention or alleviation of a cardiac disease, disorder or condition in a living animal body, including a human, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of the diphenyl urea derivative according to any one of claims 1-37.

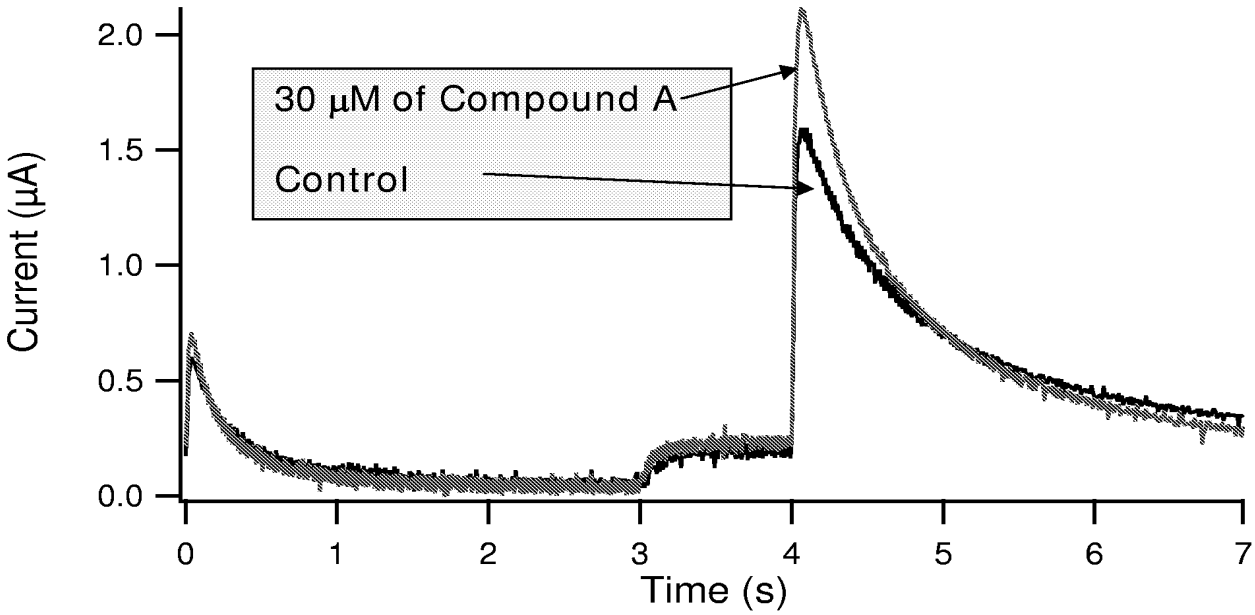
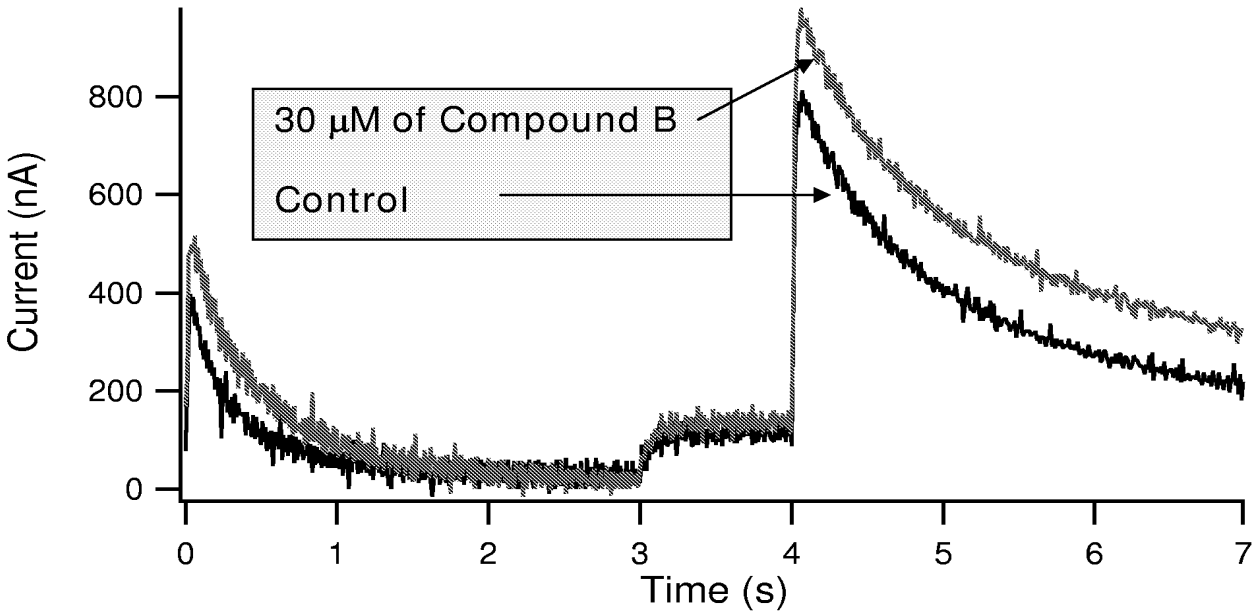

2.0
1.5
1.0
0.5
0.0
Current (µA)
30 µM of Compound A
Control
0
1
2
3
4
5
6
7
Time (s)

Fig. 1


30 µM of Compound B
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400
200
0
0
1
2
3
4
5
6
7
Time (s)

Fig. 2

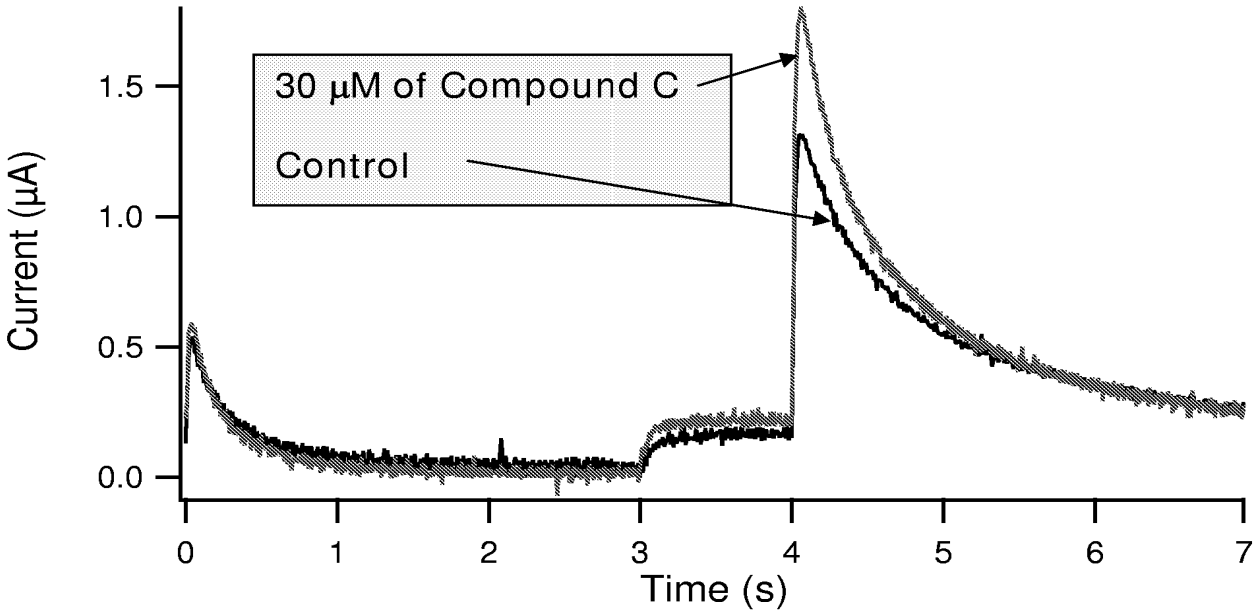
30 µM of Compound C
Control
Current (µA)
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
Time (s)

Fig. 3

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A61K 31/4439 (2006.01) *A61K 31/4196* (2006.01)
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(71) Applicant *(for all designated States except US)*: **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

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(74) Common Representative: **NEUROSEARCH A/S**; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
26 April 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIPHENYLUREA DERIVATIVES USEFUL AS ERG CHANNEL OPENERS FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

(57) Abstract: The present invention relates to the medical use of a certain group of diphenyl urea derivatives as ERG channel openers for the treatment of cardiac arrhythmias.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060093

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/41 A61K31/454 A61K31/4439 A61K31/496 A61K31/17
A61K31/4192 A61K31/4196 A61P9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI 2 September 1997 (1997-09-02), Derwent Publications Ltd., London, GB; Class 980,page 1, AN 1998-002748 XP002404359 SUZUKI RIICHI ET AL.: "Phenol derivative and its production" & JP 09 227495 A (TANABE SIYAKU CO) 2 September 1997 (1997-09-02) abstract ----- -/--	1,2,4-8, 19, 22-26, 38-41

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2006	26 -02- 2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, Elsie

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/000245 A (POSEIDON PHARMACEUTICALS AS [DK]; MADSEN LARS SIIM [DK]; DAHL BJARNE H) 3 January 2003 (2003-01-03) page 1, lines 4-7 page 7, lines 13,34-36 page 12, line 39 page 13, lines 13-28 claims 1,7,9	41
X	WO 94/22807 A (NEUROSEARCH AS [DK]; OLESEN SOEREN PETER [DK]; MOLDT PETER [DK]; PEDER) 13 October 1994 (1994-10-13) cited in the application page 1, paragraph 2 page 4, paragraph 4 - page 5, paragraph 2 page 8, paragraph 2 - page 11, paragraph 4 page 19, paragraph 4 page 27, paragraph 1 claims 8-10	41
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A	EP 0 790 240 A (TANABE SEIYAKU CO [JP]) 20 August 1997 (1997-08-20) page 2, line 46 - page 5, line 14 examples 4,5,7,14,20,24-26,36,257 claim 1	1,2,4-8, 11,14, 15,17, 19, 22-25, 38-41

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/012254 A (ARENA PHARM INC [US]; TEEGARDEN BRADLEY [US]; JAYAKUMAR HONNAPPA [US];) 10 February 2005 (2005-02-10) page 1, lines 9-17 table A; compounds 107,158,159,164,165,168,169,172,173,179,180,184 compounds 185,188,189,193,194 page 76, line 4 - page 77, line 24 claims 1,42	1,2,4-8, 11, 14-17, 19, 22-26, 38-41
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P,X	WO 2005/092843 A (NEUROSEARCH AS [DK]; DAHL BJARNE H [DK]; PETERS DAN [DK]; OLSEN GUNNAR) 6 October 2005 (2005-10-06) page 1, line 38 - page 3, line 2 page 8, lines 1-28 page 10, lines 16,28,37,38 page 14, line 34 - page 15, line 3 compounds 1A,1B,1C,1K,4A claims 1,27,32,33	1,2,5-8, 11, 14-16, 19, 22-25, 38-41

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HANSEN, RIE SCHULTZ ET AL: "Activation of human ether -a-go-go- related gene potassium channels by the diphenylurea 1,3-bis-(2-hydroxy-5-trifluoromethyl-phenyl)-urea (NS1643)" MOLECULAR PHARMACOLOGY , 69(1), 266-277 CODEN: MOPMA3; ISSN: 0026-895X, 2006, XP008069762 abstract page 267, column 1, paragraph 3 - column 2, paragraph 2 figure 1 page 274, column 2, paragraph 2 page 276, column 2, paragraphs 1,2 -----	1,2,4-7, 11, 14-16, 38-41
E	WO 2006/064015 A2 (NEUROSEARCH AS [DK]; DAHL BJARNE H [DK]; CHRISTOPHERSEN PALLE [DK]; DE) 22 June 2006 (2006-06-22) page 3, line 6 - page 4, line 16 page 36, lines 21-33 claims 1,2,4-8,11,14-18,20,23-26,39 -----	41
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/060093

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 41 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-2, 4-8, 11, 14-17, 19, 22-25 (all partially), 26 (entirely), 38-41 (partially)

   The use of a diphenyl urea derivative represented by Formula I or a pharmaceutically acceptable salt thereof, wherein X represents hydroxy for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of an abnormal heart rhythm.
   A method of treatment, prevention or alleviation of a cardiac disease, disorder or condition in a living animal body, which comprises the step of administering such a diphenyl urea derivative.

   ---

2. claims: 1-2, 4-8, 11, 14-17, 19, 22-25 (all partially), 27-28 (entirely), 38-41 (partially)

   The use of a diphenyl urea derivative represented by Formula I or a pharmaceutically acceptable salt thereof, wherein X represents carboxy for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of an abnormal heart rhythm.
   A method of treatment, prevention or alleviation of a cardiac disease, disorder or condition in a living animal body, which comprises the step of administering such a diphenyl urea derivative.

   ---

3. claims: 1-9 (partially), 10 (entirely), 11-12 (partially), 13 (entirely), 14, 17-20 (all partially), 21 (entirely), 22-23 (partially), 29 (partially), 30-33 (entirely), 38-41 (partially)

   The use of a diphenyl urea derivative represented by Formula I or a pharmaceutically acceptable salt thereof, wherein X represents a tetrazolyl group for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of an abnormal heart rhythm.
   A method of treatment, prevention or alleviation of a cardiac disease, disorder or condition in a living animal body, which comprises the step of administering such a diphenyl urea derivative.

   ---

4. claims: 1-9, 11-12, 14, 17-20, 22-23, 29 (all partially), 34-35 (entirely), 38-41 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The use of a diphenyl urea derivative represented by Formula I or a pharmaceutically acceptable salt thereof, wherein X represents an oxadiazolyl group for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of an abnormal heart rhythm.
A method of treatment, prevention or alleviation of a cardiac disease, disorder or condition in a living animal body, which comprises the step of administering such a diphenyl urea derivative.

---

5. claims: 1-9, 11-12, 14, 17-20, 22-23, 29 (all partially), 36-37 (entirely), 38-41 (partially)

The use of a diphenyl urea derivative represented by Formula I or a pharmaceutically acceptable salt thereof, wherein X represents a triazolyl group for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of an abnormal heart rhythm.
A method of treatment, prevention or alleviation of a cardiac disease, disorder or condition in a living animal body, which comprises the step of administering such a diphenyl urea derivative.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/060093

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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